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(54) Taste mask coating for preparation of chewable pharmaceutical tablets.

(57) Chewable medicament tablets are made from coated granules of a medicament wherein the coating comprises a mixture of methylaminoethyl methacrylate and neutral methacrylic acid ester and a cellulose ester, e.g. cellulose acetate, cellulose acetate butyrate, cellulose triacetate or a combination thereof and optionally polyvinyl pyrrolidone and a process for making such tablets and a method of providing taste masking and sustained releasing of medicaments utilizing such coatings.

EP 0 523 847 A1

FIELD OF THE INVENTION

This invention relates to tablets containing means to mask the taste of active ingredients. More particularly, the taste masking of active ingredients is achieved by coating a pharmaceutical active material with a reverse enteric polymer coating system.

Orally administered medicaments are given to the patient in many forms, such as liquid solutions, emulsions, or suspensions, or in solid form such as capsules or tablets (as used herein, the term "tablet" means any shaped and compressed solid dosage form, including caplets). Medicaments administered in tablet or capsule form are usually intended to be swallowed whole. Therefore, the often disagreeable taste of the active ingredient need not be taken into account in formulating the medicine, except for the provision of means to prevent the taste from being apparent during the short time that the medicine is in the mouth. Such means may include the provision of an appropriately thin and quickly dissolving coating on the tablet, the use of the gelatin capsule form (the gelatin outer shell of the capsule keeps the active ingredient inside until the capsule has been swallowed), or simply compressing a tablet firmly so that it will not begin to disintegrate during the short time that it is intended to be in the mouth.

Children, older persons, and many other persons have trouble swallowing whole tablets and even capsules. Therefore, in cases where the dosage to be administered cannot be made into a very small tablet or capsule, it is desirable to provide the medicine either in liquid form or in a chewable solid form, in addition to the tablet or capsule that is designed to be swallowed whole. Even where the medicine can be formulated as a liquid, it is desirable also to be able to provide a chewable solid form (i.e. tablets) because of added convenience versus carrying a supply of liquid medicine.

A common problem with chewable tablet forms is the often disagreeable taste of the active ingredient which manifests itself during chewing. In some cases, the taste of the active medicament in a tablet can be overpowered by adding flavoring ingredients to the tablet so that when it is chewed, the taste of the active ingredient is simply overpowered. For instance, this has been done with children's aspirin where the dosage is small enough so that the amount of flavoring agents needed to mask the taste of the medicine is not so great that the tablet becomes unreasonably large. A different approach is taken with a commercially available children's size tablet of acetaminophen (acetyl para-aminophenol or "APAP") wherein the APAP is present in granules that are coated with ethyl cellulose. A significant proportion of the APAP remains shielded by the coating (and therefore does not contribute to taste) while the tablet is in the mouth, despite some breakage of the ethyl cellulose coating during compression of the tablet and some additional breakage of the coating during chewing. The APAP becomes bioavailable via permeation through the coating (although ethyl cellulose is not soluble in aqueous fluids, water does permeate through the coating) and from the granules where the coating is broken.

Examples of taste masked coating systems are disclosed in the following references. U.S. Patent No. 4,851,226, issued July 25, 1989, discloses chewable medicament tablets wherein granules of active ingredient are directly coated with a blend of cellulose acetate or cellulose acetate butyrate and polyvinylpyrrolidone. EP-A-0 411 952 discloses chewable medicament compositions comprising a rotogranulation blend of from about 88 to about 97.5% medicament, about 2 to about 10% polyvinylpyrrolidone (PVP) and about 0.5 to about 2.0% sodium lauryl sulfate (SLS), by weight of the weight of the total composition. In further embodiments a coating of hydroxyethyl cellulose (HEC) or a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose (HPMC) is added to these rotogranulated particles. EP-A-0 459 695 discloses a chewable medicament comprising a coating for active medicament comprising a polymer blend of cellulose acetate and/or cellulose butyrate and water soluble hydroxypropyl cellulose to provide a taste masked and/or sustained release coating.

The present invention is directed to the discovery of a reverse enteric coating process for active medicaments which can achieve a better balance between taste masking, dissolution and rate of bioavailability than other previously known coating combinations.

SUMMARY OF THE INVENTION

As embodied and fully described herein, the present invention provides a chewable tablet of a medicament comprising a pharmaceutical active coated with a taste masking effective amount of a polymer blend of at least 5% by weight of a blend of methylaminoethyl methacrylate and neutral methacrylic acid ester (MM/MAE) and a cellulose ester. Preferably the cellulose ester is at least one of cellulose acetate (CA), cellulose acetate butyrate (CAB) or cellulose triacetate (CTA). In preferred embodiments of the invention, the polymer blend additionally comprises polyvinylpyrrolidone (PVP) and/or 2-vinylpyridine(V)-/styrene(S) copolymer in a polymer ratio of about 65/35 or 80/20 (V/S).

In further preferred embodiments, the medicament coated is selected from the group consisting of acetaminophen (APAP), ibuprofen, ibuprofen sodium, dexibuprofen lysinate, naproxen, naproxen sodium, and other similar NSAID's. psyllium, and the general class of antihistamines (e.g. chlorpheniramine, astemizole) gastrointestinal drugs (e.g. famotidine, loperamide, ranitidine and cimetidine) and decongestants (e.g. pseudoephedrine). The medicament is preferably directly coated or rotogranulated if their physical shape (e.g. irregular) or size (e.g. small) discourages uniform coating. The polymer coating comprises about 2 to 25% preferably 8 to 16% by weight of the total weight of the coated medicament composition. The coated particles may then be compressed into tablet form together with excipients and flavoring agents to produce chewable tablets.

The invention also provides a process of coating medicaments and methods of using the coated medicaments to make taste masked and/or sustained release chewable tablets.

DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described specifically in terms of its most preferred embodiments which are the preparation of reverse enteric coated granulations of medicaments and chewable tablets comprising coated granules of medicament. Reference will also be made in detail herein to other preferred embodiments of the compositions, processes and methods of the invention.

Reverse enteric coatings are defined herein as coatings which are not water soluble at non-acidic pH, e.g., in the mouth, but rather are soluble in the fluids of the gastrointestinal tract at lower pH's, i.e., pH 1.0 to about 3.5-4.0, e.g., in the stomach. Application to taste masking use of this pH solubility profile of coated medicaments to taste masking is possible because of the initial insolubility of the coating in the mouth and subsequent ready release and bioavailability of the medicament in the acid medium of the gut or stomach where the coating is soluble.

In accordance with a preferred embodiment of the invention the polymer blend utilized comprises both a cellulose acetate (CA) and a MM/MAE component. Separately, the solubility of the CA component is pH independent and the MM/MAE component is pH dependent. Combining the two polymers in various ratios will cause the subsequently formed polymer film coat to be more or less prone to diffusion of solute, porous to solute and/or soluble in solute. The degree of diffusion, porosity and/or solubility of the film coat depends on the ratio of CA:MM/MAE and the physicochemical properties of the drug to be taste masked.

This pH sensitivity is introduced to the polymer blend upon the addition MM/MAE such that at pH's less than 3.5-5.0 the polymer blend film becomes porous due to the formation of polymeric salts which are more soluble than MM/MAE resulting in more drug release. Approaching the neutral to weakly alkaline range (pH 5.0-6.0), the MM/MAE, rather than forming soluble polymeric salts, begins to swell and becomes more permeable to water (diffusion). At pH 6-7, as is encountered in the mouth, MM/MAE films are resistant to solubility and are taste proof for approximately 30-60 seconds since it takes at least this long for water to diffuse through the polymer film coat.

From a physicochemical perspective, if the drug of interest is relatively water soluble the relative amount of CA would have to be increased in order to taste mask the drug in the mouth. If the drug of interest is less water soluble the relative amount of CA would be lower in order to attain the same degree of taste masking seen with the more water soluble drug.

The polymer blend of CA and MM/MAE is also advantageous in enhancing the durability of coated particles when compressed, since MM/MAE used alone is not a highly durable film due to its relatively brittle nature. MM/MAE used alone is likely to be broken during compression and/or during chewing of the tablet, whereas the polymer blend of CA and MM/MAE is more flexible and less likely to be broken.

The coating process is also made easier with the polymer blend of the invention versus use of MM/MAE alone. MM/MAE in the presence of residual solvent can develop tackiness during processing. High tackiness during processing leads to increased particle-particle sticking. Particle agglomeration decreases efficiency of coating leading to erratic drug release profiles from batch to batch. In addition, if tackiness occurs extensively the granulation will ball up into one solid mass and further processing would not be possible. Used in combination with CA or CAB this tackiness is reduced and processing is improved.

In accordance with preferred embodiments of the invention granules of medicament are reverse enteric coated directly. In cases where the raw medicament is of irregular shape or small size the raw medicaments are first rotogranulated to produce nearly spherical granulated particles and then coated. These rotogranulated particles are preferably in the size range of about 150 to 400 microns and are more readily coated to produce a more uniform coating for superior taste masking and sustained releasing applications.

Details of a preferred process of rotogranulating and subsequent fluid-bed coating are provided in the examples section. Preferred methods are further described in: Jones, D. M. "Factors to Consider in Fluid-

Bed Processing," Pharmaceutical Technology, April 1985, Pg. 50-63; and Jager, K. F. et al., "Effect of Material Motion on Agglomeration in the Rotary Fluidized-Bed Granulator", Drugs Made in Germany, Vol. XXV, Pg. 61-65 (1982). The entire disclosure of these articles are hereby incorporated herein by reference. Granulations comprising famotidine, PVP and lactose produced by rotogranulation are disclosed in EP-A-0 473 431.

Rotogranules have increased strength due to the compaction or densification of the granulation mixture as rotogranules are formed by rotation in the rotogranulator bed. This resistance to breakage is advantageous since broken particles are of a smaller size and are not readily coated in subsequent coating steps. Smaller sized particles without proper coating detract from the taste masking purpose of the coating by providing poor taste to the mixture as a whole. Further, smaller sized particles tend to agglomerate and interfere with subsequent fluid bed coating operations.

For some medicaments, including acetaminophen, rotogranulation may not be a necessary preparatory step to produce desirable coated medicaments in accordance with the invention. The process and materials of the invention are applicable as coatings for a wide variety of medicaments which are preferably released in the gut or upper G-I tract and these include but are not limited to acetaminophen (APAP), ibuprofen, ibuprofen sodium, dexibuprofen lysinate, naproxen, naproxen sodium, and other similar NSAID's and their salts, psyllium, and the general class of antihistamines (e.g. chlorpheniramine, astemizole) gastrointestinal drugs (e.g. loperamide and famotidine) and decongestants (e.g. pseudoephedrine) as well as salts and combinations thereof.

In preferred embodiments of the compositions and processes of the invention, medicament, preferably raw or in rotogranular form, is coated with a polymer blend of from about 5 to 95% MM/MAE and 5 to 95% of a cellulose ester, preferably CA, CAB, CTA or a combination thereof. The coated granules, together with other ingredients such as flavoring agents, extenders, excipients, and the like, are compressed into tablet form.

Cellulose esters such as cellulose acetate and cellulose acetate butyrate, and cellulose triacetate are quite water insoluble but are soluble in organic solvents. They can provide good taste masking properties since they do not dissolve in the mouth and are tough enough to remain effectively intact during processing and normal chewing in the mouth. If used alone, however, a poorly soluble cellulose ester coating would not provide adequate ready release and bioavailability of the active ingredient after swallowing the chewed tablet. To provide the requisite ready release and bioavailability in the digestive tract and particularly in the acid medium of the stomach, MM/MAE is added to the polymer blend coating mixture.

The preferred MM/MAE used in accordance with the present invention is identified by its tradename EUDRAGIT™ E-100. "E-100" signifies that the polymer EUDRAGIT E is a solid and MM/MAE is present in 100% in that solid, whereas, EUDRAGIT E 12.5 is a lacquer solution containing 12.5% MM/MAE. EUDRAGIT E brand acrylic resin is a copolymer based on dimethylaminoethyl methacrylates and neutral methacrylic acid esters with a mean molecular weight of 150,000, a viscosity of mPa.s : 3-12 at 20° C, a refractive index of N_D^{20} : 1.380-1.385 and a relative density of d_4^{20} : 0.810-0820.

Further, other additives such as PVP may be added to the polymer blend coating. PVP is a polymer which is soluble in both water and organic solvents. The water solubility of PVP provides bioavailability of the coated active medicament in the gastrointestinal (GI) tract. When the coated granules are swallowed, the active medicament becomes bioavailable via permeation as the coating disintegrates. Permeation can occur through the intact coating but is encouraged by the disintegration of the coating which becomes porous through dissolution of the water soluble PVP and/or MM/MAE in the stomach.

The MM/MAE, cellulose ester and optionally PVP polymer blend has good mechanical flexibility which is advantageous in a product where the coating must withstand the forces of tablet compression and chewing in the mouth. Further, addition of taste neutral cellulose ester and/or PVP to poor tasting MM/MAE provides a useful taste mask coating. Use of MM/MAE alone would result in a poorly tasting chewable medicament. A high enough proportion of the coating of MM/MAE, cellulose ester and optionally PVP remains effectively intact on the medicament granules through the compression of the tablet and through normal chewing in the mouth to permit effective taste masking of unpleasant tasting medicaments. The term "effectively intact" means that the coating remains sufficiently integral to mask the taste or flavor of the medicament. This taste masking is effective to mask the unpleasant flavor of the medicament without requiring large and bulky amounts of overpowering flavoring agents.

MM/MAE, CA, CTA and CAB are not very soluble, if at all, in water, and are more conveniently applied from an organic solvent solution. Solubility of optional ingredient PVP in organic solvents permits ready mixing with MM/MAE and cellulose esters. MM/MAE, CA, CTA and/or CAB with or without PVP form clear compatible solutions in organic solvents, preferably acetone/methanol mixtures, which are suitable for pharmaceutical coating. The polymer blend of the invention provides the balance needed for good taste

masking while being chewed in the mouth, along with either rapid or sustained bioavailability of the active medicament in the GI tract after swallowing.

The coated granules may be made by coating the granules of medicament with an organic solvent solution of the polymers in a fluidized bed coating operation. A wide variety of organic solvents may be used to prepare the organic solvent solution of the coating polymers. For instance, a more preferred solvent is acetone-methanol, but other solvent systems may also be used, including preferably methylene chloride-methanol (e.g. 9:1), acetone, ethanol, and isopropyl alcohol. Other solvents include methyl alcohol, ethyl alcohol, ethyl alcohol/water 6:4, isopropyl alcohol, n-butyl alcohol, propylene glycol, ethylene glycol, monobutyl ether, acetone, methyl ethyl ketone, cyclohexanone, methylene chloride, chloroform, carbon tetrachloride, trichloroethylene, tetrachloroethylene, ethyl acetate, n-butyl acetate, propylene glycol acetate, toluene, and white spirits 100-140 • C.

The polymers are dissolved in the solvent and the polymer solution is then coated onto medicament granules or other medicament active ingredient or combination of ingredients, using a fluidized bed coater. Air (which may be heated) passes through a bed of the medicament granules to fluidize them, and the solvent solution of the two polymers is sprayed onto the fluidized bed and thereby coats the rotogranules. The air passing through the bed dries the coated rotogranules, so that a dry coated granule is obtained. The coated granules are then used in combination with various excipients, flavors, and colors to make a chewable tablet.

The dried coating usually constitutes about 2-25% of the total dry weight of the coated rotogranule. The exact proportions of coating to medicament desired for individual cases can be determined by routine experimentation. General considerations for determining coating amounts include physicochemical characteristics of the active i.e. solubility, pKa etc., composition of the granule i.e. types of excipients and their physicochemical properties, CA or CAB : MM/MAE ratio. Generally as CA or CAB is increased the sustained release effect increases and the taste masking increases. However, if the relative amount CA or CAB is increased too much the active may not be released entirely and the pH sensitivity of the blend may be lost.

The amount of coating may be varied in light of the intended application and desired bulk of the products. Chewable tablets can be acceptable in larger sizes than swallowed tablets since chewing will reduce the size of the tablets in the mouth. Larger proportions of coating may be used to provide a sustained releasing or better tasting formulation.

When two or more medicaments are utilized in tablets of the present invention the coatings may be varied to provide a slower release of one medicament over another. This is especially advantageous for dosing a combination of medicaments that are more effectively released in different parts of the digestive tract or are better released separately in the digestive tract to avoid interference with each other or other incompatibility. Further, the same medicament may be subject to different coating compositions and amounts to provide for sustained release of some portion of the medicament and immediate release of another portion of the medicament to achieve an optimal dosing versus time profile. Obtaining such optimal dosing/time profiles depends upon the particular medicaments and medical needs required. The exact proportions of coating materials used to achieve these profiles can be determined by routine experimentation.

As a general rule, the proportion of polymer in solution will be preferably from about 5 to 18 or 20, more preferably about 5 to 14 and most preferably about 10 weight percent, depending upon the process parameters. As a practical matter, a concentration of less than 5% polymer blend would unduly lengthen the coating process and a concentration of more than 18 to 20% would hamper spraying of the thickened solution.

While exact size of the coated rotogranules has not been found to be critical, the coated granules are preferably sized in the range of 150 to 400 microns. Particle sizes of less than 150 microns are difficult to coat and particle sizes of greater than 400 microns may provide undesirable grittiness to the finished product. In general, particles of like size facilitate blending and provide regularity to dosage forms.

Further, the coating of the invention provides a convenient means for providing a viable dosage form for combination medicaments which are incompatible before (e.g. during storage) or after administration.

An illustrative preferred procedure for coating the rotogranules of medicament in accordance with the invention is briefly described here and provided in more detail in the following examples section. The medicament, in rotogranular form, is preferably placed in a fluidized bed coater and is fluidized by a flow of warm air. The temperature of the air has not been found to be narrowly critical, and can vary over a wide range, keeping in mind the fact that the temperature should not be high enough to cause decomposition, sintering, or melting of the medicament granules. When coating various rotogranules, a product temperature of from about 20 • to 40 • C, preferably 25 • to 35 • C is maintained. The rate of air flow is adjusted so as to

fluidise the granules. Such flow will vary on factors such as the specific equipment used, the size of the charge of granules, the size of the individual granules, and other factors that are known to those skilled in the art of fluidized bed coating. The air temperatures are monitored to provide an increase in temperature of the inlet air from 35 ° C to 65 ° C during the coating run. The outlet air is maintained at approximately 25 ° C to 35 ° C during the coating run. These temperatures may vary with different polymer blend ratios or with different actives.

After the medicament has been fluidized, the polymer solution is sprayed via bottom, top or tangential spray onto the fluidized bed. The air flow through the bed is continued until the amount of solvent remaining in the coating has been greatly reduced. The rotogranules are actually dry to the touch within a very short time after the coating solution has been sprayed onto the granules of medicament; a matter of a few seconds in some cases. The total drying time required to ensure that the solvent content of the coating has been reduced to the level desired may take much longer, depending on the solvent used, temperature of the air, size of the batch, and the like. Routine experimentation will suffice to determine the appropriate air temperatures and total times required in the fluidized bed coaters in individual cases.

The invention will now be illustrated by examples. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the present invention and an outline of a process for preparing the rotogranule compositions and chewable medicament tablets of the invention.

EXAMPLES

The Examples below set forth the ingredients and proportions for typical laboratory scale preparations of coated medicament granules.

The coating methods used are disclosed for example in Jones, D. M. "Factors to Consider in Fluid-Bed Processing" Pharmaceutical Technology, April 1985 and rotogranulating methods are taught by, for example, in Jager, K. F. et al., "Effect of Material Motion on Agglomeration in the Rotary Fluidized-Bed Granulator", Drugs Made in Germany, Vol. XXV, Pp. 61-65 (1982) which have been incorporated herein by reference. The term "total coat" refers to the proportion of coating to uncoated rotogranule in the coated rotogranule product, concentration of "polymer solution" to the proportion of polymer in the organic solvent solution, and "total batch" to the weight of medicament plus coating.

EXAMPLE I

Preparation of coated granules: A coating solution of polymers as identified below is prepared by adding the polymers to the organic solvents with stirring. The material to be coated, in granular form is placed in a fluidized bed coater and is fluidized by the flow of air. The temperature of the air may be a critical factor if high concentrations of EUDRAGIT E-100 are used and should be maintained between 25 and 40 degrees Centigrade. If temperatures go below 25 degrees the granulation becomes too wet and can mass together. If the temperature goes above 40 degrees the EUDRAGIT can become tacky and cause massing of material. The rate of air flow is adjusted so as to fluidize the granules. The coating material is then sprayed using a Wurster or rotogranulator insert. After the coating process is complete the coated granules are dried for a short period of time if necessary. Normally drying is minimal since organic solvents are used which are driven off rapidly, in a few seconds, with temperatures above 25 degrees Centigrade. To be sure all organics are driven off to a safe level drying times up to 3 hours may be used. Routine experimentation will suffice to determine the appropriate air temperatures and total times required in the fluidized bed coaters in individual cases.

Total acetaminophen charge (kg):	4.000
% Solids in soln:	10.000
Total polymer (kg):	0.444
10% Excess (kg):	0.488
Total coating soln (kg):	4.880
Total solvent wt. (kg):	4.392

POLYMER NAME	%POLYMER	POLYMER WT. (kg)
A CA 398-10 (39.8% acetyl content)	15.0	0.073
B EUDRAGIT E-100 (MM/MAE)	50.0	0.244
C PVP K29-32 (Avg. M.W. of about 40,000)	35.0	0.171
TOTAL	100.0	0.488

SOLVENT	%SOLVENT	SOLVENT WT.(kg)
A Methanol	20.0	0.878
B Acetone	80.0	3.514
TOTAL	100.0	4.392

EXAMPLES II-IX

The procedure of Example I is carried out using the following ingredients:

EXAMPLE II

Total acetaminophen charge (kg):	4.000%
Solids in soln:	10.000
Total polymer (kg):	0.444
10% Excess (kg):	0.488
Total coating soln (kg):	4.880
Total solvent wt. (KG):	4.392

POLYMER NAME	%POLYMER	POLYMER WT. (kg)
A CA 398-10	85.0	0.415
B EUDRAGIT E-100	15.0	0.073
TOTAL	100.0	0.488

SOLVENT	%SOLVENT	SOLVENT WT. (kg)
A Methanol	20.0	0.878
B Acetone	80.0	3.514
TOTAL	100.0	4.392

EXAMPLE III

Total acetaminophen charge:	4.000
% Solids in soln:	10.000
Total polymer (kg):	0.444
10% Excess (kg):	0.488
Total coating soln (kg):	4.880
Total solvent wt. (kg):	4.392

POLYMER NAME	% POLYMER	POLYMER WT. (kg)
A CA 398-10	60.0	0.293
B EUDRAGIT E-100	40.0	0.195
TOTAL	100.0	0.488

SOLVENT	%SOLVENT	SOLVENT WT.(kg)
A Methanol	20.0	0.878
B Acetone	80.0	3.514
TOTAL	100.0	4.392

EXAMPLE IV

Total acetaminophen charge:	4.000%
Solids in soln:	10.000
Total polymer (kg):	0.444
10% Excess (kg):	0.488
Total coating soln (kg):	4.880
Total solvent wt.(kg):	4.392

POLYMER NAME	%POLYMER	POLYMER WT. %
A CA 398-10	40.0	0.195
B EUDRAGIT E-100	60.0	0.293
TOTAL	100.0	0.488

SOLVENT	% SOLVENT	SOLVENT WT. (kg)
A Methanol	20.0	0.878
B Acetone	80.0	3.514
TOTAL	100.0	4.392

EXAMPLE V

Total acetaminophen charge:	4.000
% Solids in soln:	10.000
Total polymer (kg):	0.444
10% Excess (kg):	0.488
Total coating soln (kg):	4.880
Total solvent wt. (kg):	4.392

POLYMER NAME	% POLYMER	POLYMER WT. (kg)
A CA 398-10	25.0	0.122
B EUDRAGIT E-100	75.0	0.366
Total	100.0	0.488

SOLVENT	%SOLVENT	SOLVENT WT. (kg)
A Methanol	20.0	0.878
B Acetone	80.0	3.514
TOTAL	100.0	4.392

EXAMPLE VI

Total acetaminophen charge:	4.000 %
Solids in soln:	10.000
Total polymer (kg):	0.444
10% Excess (kg):	0.488
Total coating soln (kg):	4.880
Total solvent wt. (kg):	4.392

POLYMER NAME	% POLYMER	POLYMER WT. (kg)
A CA 398-10	15.0	0.073
B EUDRAGIT E-100	85.0	0.415
TOTAL	100.0	0.488

SOLVENT	% SOLVENT	SOLVENT WT. (kg)
A Methanol	20.0	0.878
B Acetone	80.0	3.514
TOTAL	100.0	4.392

EXAMPLE VII

Total ibuprofen rotogranule charge (kg):	4.000
% Solids in soln:	10.000
Total polymer (kg)	0.444
10% Excess (kg):	0.488
Total coating soln (kg):	4.880
Total solvent wt. (kg):	4.392

POLYMER NAME	% POLYMER	POLYMER WT. (kg)
A CA 398-10	20.0	0.098
B PVP K-29/32	40.0	0.195
C EUDRAGIT E-100	40.0	0.195
TOTAL	100.0	0.488

SOLVENT	% SOLVENT	SOLVENT WT. (kg)
A Methanol	20.0	0.878
B Acetone	80.0	3.514
TOTAL	100.0	4.392

EXAMPLE VIII

Total loperamide rotogranule charge (kg):	4.000%
Solids in soln:	10.000
Total polymer (kg):	0.444
10% Excess (kg):	0.488
Total coating soln (kg):	4.880
Total solvent wt. (kg):	4.392

POLYMER NAME	%POLYMER	POLYMER WT. (kg)
A CA 398-10	20.0	0.098
B PVP K-29/32	40.0	0.195
C EUDRAGIT E-100	40.0	0.195
TOTAL	100.0	0.488

SOLVENT	%SOLVENT	SOLVENT WT. (kg)
A Methanol	20.0	0.878
B Acetone	80.0	3.514
TOTAL	100.0	4.392

EXAMPLE IX

Total famotidine rotogranule charge (kg):	4.000
% Solids in soln:	10.000
Total polymer (kg):	0.444
10% Excess (kg):	0.488
Total coating soln (kg):	4.880
Total solvent wt. (kg):	4.392

POLYMER NAME	POLYMER	POLYMER WT. (kg)
A CA 398-10	60.0	0.293
B PVP K-29/32	10.0	0.049
C EUDRAGIT E-100	30.0	0.146
TOTAL	100.0	0.488

SOLVENT	%SOLVENT	SOLVENT WT (kg)
A Methanol	20.0	0.878
B Acetone	80.0	3.514
TOTAL	100.0	4.392

EXAMPLE X

The functions of several ingredients utilized in this Example X and some typical replacements for them are as follows:

Mannitol is a sweetener which can be replaced by dextrose, fructose, sorbitol, compressible sugar, and/or lactose;

Microcrystalline cellulose is used to improve tablet properties.

Aspartame is an artificial sweetener which can be replaced with others such as saccharin;

Magnesium stearate is a lubricant (to lubricate the dye walls and punches used during the tablet compression procedure). It can be replaced by talc, stearic acid, calcium stearate, zinc stearate, leucine, glycerides, sodium stearyl fumarate or the like; and

Artificial and natural flavor agents can be any conventional artificial and natural flavoring agents and flavor enhancers such as vanilla, grape, peppermint, orange, cherry, and/or spearmint flavors and conventional flavor enhancers or sweeteners.

PREPARATION OF CHEWABLE TABLETS

The ingredients displayed below were dry blended, and compressed by standard procedures into round (disc shaped) chewable tablets, each weighing 385 mg. Each tablet contained 80 mg. of active acetaminophen per tablet from coated raw granules prepared in accordance with the procedure of Example I containing 10 weight percent coating of a polymer blend of 50% MM/MAE, 15% CA, and 35% PVP. Preparation of Chewable Tablets: The following materials (excluding the coated APAP) are dry blended and then compressed into tablets.

Mannitol	1749.3 g
Microcrystalline Cellulose	210.0 g
Aspartame	35.0 g
Citric Acid Anhydrous	14.7 g
Prosweet	8.4 g
Flavor	27.3 g
Magnesium Stearate	27.3 g
APAP (coated)	697.18 g (1)

(1). Based on 19.7% coat for 7000 tablets at 395mg/tablet.

The scope of the present invention is not limited by the description, examples and suggested used herein and modifications can be made without departing from the spirit of the invention. For example, other components may be added to the tablets including additional actives, various flavorings, preservatives and other pharmaceutical excipients. The present invention may also be used to provide a chewable form for vitamins, minerals or other nutrients.

Application of the compositions and processes of the present invention for medical and pharmaceutical uses can be accomplished by any clinical, medical and pharmaceutical methods and techniques as are

presently and prospectively known to those skilled in the art. Thus it is intended that the present invention cover the modifications and variations of this invention, provided that they come within the scope of the appended claims and their equivalents.

Claims

1. A chewable tablet of a medicament comprising a pharmaceutical active composition coated with a taste masking effective amount of a polymer blend of at least 5 weight percent by total weight of the polymer blend of methylaminoethyl methacrylate and neutral methacrylic acid ester and at least one cellulose ester, such as cellulose acetate, cellulose acetate butyrate, cellulose triacetate or a combination thereof.

2. The chewable tablet of claim 1 wherein the polymer blend additionally comprises polyvinylpyrrolidone or 2-vinyl pyridine styrene copolymer.

3. The chewable tablet of claim 1 or claim 2 wherein the coating mixture has a weight ratio in the range of from 95 : 5 to 5 : 95 of methylaminoethyl methacrylate and neutral methacrylate acid ester to the at least one cellulose ester.

4. The chewable tablet of any one of claims 1 to 3 wherein the amount of polymers in the coating polymer blend by weight % is 10 to 90% of methylaminoethyl methacrylate and neutral methacrylic acid ester, 10 to 90% of the at least one cellulose ester and 0 to 50% polyvinylpyrrolidone by weight of the total weight of the polymer blend.

5. The chewable tablet of any one of claims 1 to 4 wherein the pharmaceutical active composition to be coated are substantially spherical in shape.

6. The chewable tablet of any one of claims 1 to 5 wherein the medicament is selected from the group consisting of acetaminophen, ibuprofen, dexibuprofen lysinate, naproxen, naproxen sodium, psyllium, chlorpheniramine, astemizole, loperamide, famotidine, ranitidine, cimetidine, pseudoephedrine and salts and combinations thereof.

7. The chewable tablet of claim 6 wherein the tablet additionally comprises pharmaceutical excipients.

8. The chewable tablet of any one of claims 1 to 7 wherein the polymer blend comprises a sustained releasing effective amount of polymer coating.

9. The chewable tablet of any one of claims 1 to 8 wherein the polymer blend coating comprises from about 2 to 25% by weight of the total weight of the coated pharmaceutical active.

10. A method of preparing a chewable medicament tablet comprising the steps of:
    preparing a granulation composition of a medicament;
    coating the medicament granulation composition with a polymer blend of 5 to 95% methylaminoethyl methacrylate/neutral methacrylic acid ester and 5 to 95% of a cellulose ester; and
    forming a chewable tablet by compressing the coated medicament composition in the presence of excipients.

11. A method for taste masking medicaments comprising coating a medicament composition with a taste masking effective amount of a polymer blend comprising from about 5 to 95% methylaminoethyl methacrylate/neutral methacrylic acid ester and 5 to 95% of a cellulose ester.

12. The process of claim 10 or claim 11 wherein the cellulose ester is selected from the group consisting of cellulose acetate, cellulose acetate butyrate, cellulose triacetate or a combination thereof.

13. The process of any one of claims 10 to 12 wherein the polymer coating comprises from 2 to 25% by weight of total weight of the coated composition.

14. The process of any one of claims 10 to 13 wherein the polymer blend additionally comprises polyvinylpyrrolidone.

15. The method of any one of claims 10 to 14 wherein the coated medicament is selected from the group consisting of acetaminophen, ibuprofen, ibuprofen sodium, dexibuprofen lysinate, naproxen, naproxen sodium, psyllium, chlorpheniramine, astemizole, loperamide, famotidine, ranitidine, cimetidine, pseudoephedrine and salts and combinations thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 92 30 5397

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y D	EP-A-0 317 274 (MC NEIL CONSUMER PRODUCTS COMPANY) * the whole document * & US-A-4 851 226	1-15	A61K9/00 A61K9/50
Y	EP-A-0 077 264 (A.E.C.- SOCIÉTÉ DE CHIMIE ORGANIQUE ET BIOLOGIQUE) * page 1, line 1 - line 5 * * page 2, line 1 - page 3, line 18 * * page 7 - page 12; examples 1-6 *	1-15	
Y	EP-A-0 101 418 (ASTRA LÄKEMEDEL AKTIEBOLAG) * page 8; example 2 * * page 11; example 5 *	1-15	
Y	EP-A-0 378 137 (KALI-CHEMIE PHARMA GMBH) * the whole document *	1-15	
Y	DATABASE WPIL Week 8921, Derwent Publications Ltd., London, GB; AN 89-156775 & JP-A-1 100 116 (MITSUI TOATSU CHEM INC) * abstract *	1-15	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A61K
Y	DATABASE WPIL Week 8937, Derwent Publications Ltd., London, GB; AN 89-266836 & JP-A-1 193 215 (EISAI KK) * abstract *	1-15	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	07 OCTOBER 1992	BENZ K.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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